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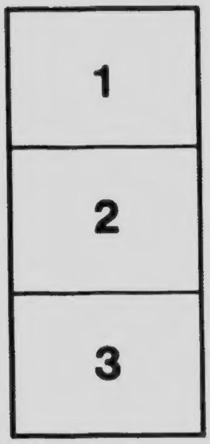

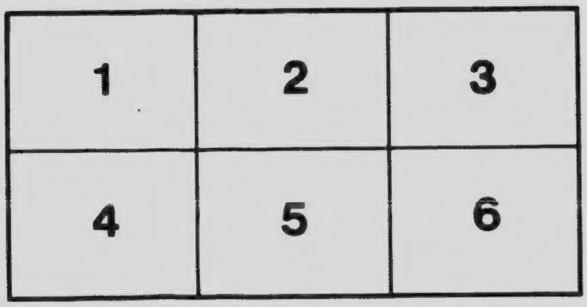

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PHYSIOLOGICAL SERIES

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No. 15: THE MECHANISM FOR VASODILATATION FROM ADRENALIN, BY FRANK A. HARTMAN and LOIS McPHEDRAN FRASER

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FURTHER OBSERVATIONS ON THE DIFFERENTIAL ACTION OF ADRENALIN

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Received for publication March 17, 1917

In the course of a series of experiments performed by one of us and reported in this Journal (1), it was found that the fall in general blood pressure, which is caused by the intravenous injection of small doses of adrenalin, is not brought about by dilatation in the vessels of all parts of the body alike. In an animal in which the arteries to the abdominal organs have been clamped, injections of a standard small dose of adrenalin caused much the same fall as had previously occurred in the intact circulation. On the other hand, when the arteries to the limbs were occluded, those to the splanchnic area being intact, the reaction to the standard dose was changed from a pure fall to a rise of blood pressure, as registered from the carotid artery. In that research the only distinction drawn was the broad one as between the reactions of the "peripheral" circulation on the one hand, which included the vessels of bone, muscle, and skin, and that of the "splanchnic" circulation on the other, which, as well as comprising the vessels of the abdominal and thoracic viscera, necessarily included those of the muscles of the thorax and back. The present research was undertaken with a view to following out the subject of the differential action of adrenalin somewhat more in detail, and in the hope of arriving at some conclusion as to the mechanism involved in the vascular adjustment caused by it.

Oncometric experiments were carried out on intestine, spleen, and kidney. While our research was in progress the appearance of the paper by Hoskins, Gunning and Berry (2) made further investigation of the reactions in skin and muscle unnecessary.

In every case simultaneous records were taken of the reactions of at least two organs in response to adrenalin, since we considered it of importance to determine whether the same range of dose which caused constriction in any one abdominal organ also caused constriction in all the others, and whether the amount giving rise to dilatation in one was necessarily the same as that which caused another to dilate. Since the reaction of any organ to a given dose may vary not only among different individuals, but also in the same individual during the period of an experiment, it is necessary to record the changes occurring in the same animal, at the same time.

The animals used were dogs and cats. In two of the experiments on the latter we injected urethane subcutaneously; in all the others the anesthetic was ether. Blood pressure was registered from the right carotid artery. Injections of adrenalin were made with a graduated syringe, the needle of which was thrust through the wall of a piece of rubber tubing fitted to a cannula, which was inserted low in the left jugular vein. The adrenalin solution used was that manufactured by Parke, Davis and Company, 1 : 1,000, diluted with distilled water to the required strength immediately before use. In each experiment the first injections were made of a solution 1 : 100,000; when large doses were required, as was often the case in working with dogs, in preference to injecting large quantities of distilled water into the animal's circulation, we substituted for the more dilute solution one of a strength of 1 : 10,000. The duration of each injection was signaled on the record below the time marker. No special precautions were taken as to absolute uniformity in the rate of injection, but it was kept fairly constant, and was in all cases slow, as shown by the records.

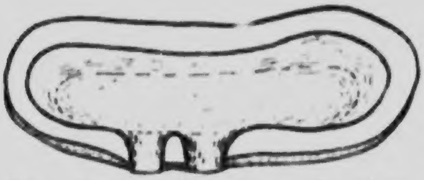
Fig. 1. Gutta percha oncometer for spleen

In some experiments we left the vagi intact; in the majority they were cut. We were unable to observe, however, any specific effect of these on the reaction of any organ to adrenalin except the familiar one of cardiac inhibition caused by large doses, with the consequent great rise in blood pressure.

The oncometers which we used for kidney and for intestine were gutta percha ones of the ordinary type, fitted with glass lids. The early experiments on the spleen were done with the same oncometers; later we had a series of special ones made. These were modelled after the shape of the spleen (see fig. 1) and were provided with two lips for stalks, separated by about 0.6 cm. in the smaller and 1.5 cm. in the larger.

As recorders in the first few experiments we used Marey's drums;

later we substituted for these bellows recorders, which have the advantage of recording volume changes without introducing alterations of pressure within the system itself. In several experiments the recorders were calibrated by injections of known volumes of air.

The pressure inside the system varied little from atmospheric; in practice we raised the pressure until the bellows were about half filled, and were thus adjusted to give maximum variations in either direction.

INTESTINE

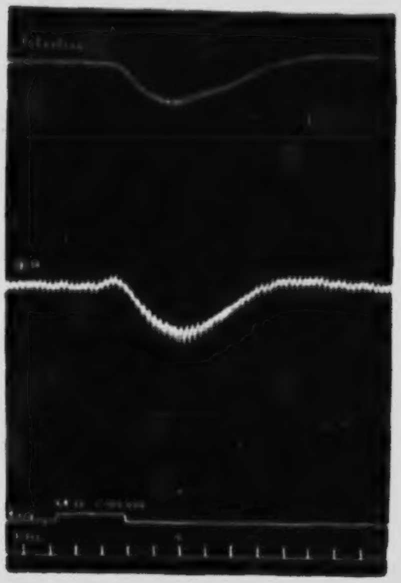

Fig. 2. Constriction of the intestine following injection of a small dose of adrenalin (0.4 cc., 1 : 100,000). Dog 14 (Reduced ½)

A loop of the small intestine, about one-third of its total length, was selected, generally that immediately above the caecum, since the blood vessels there are long and form a convenient stalk. Two pairs of double ligatures were tied about its lower end, about 2 inches apart, the blood vessels supplying the piece between the ligatures tied off, and the piece of intestine removed. A similar operation was performed at the upper end of the required length, and the loop was ready to be placed in the oncometer without the necessity of further dissection, other than simply slitting the mesentery for an inch or two on either side of the stalk. Before putting the loop into the oncometer we washed out its contents with warm saline. This prevents the slow formation of gas which otherwise takes place within the lumen, and which interferes with the records of volume changes due to the circulation alone. The whole operation from the time the abdomen was opened until the intestine was put into the oncometer was not longer than fifteen or twenty minutes. During this time the intestinal loop and the other abdominal contents were kept covered with warm saline pads.

In the great majority of cases, the effect of doses of adrenalin, both large and small, was to cause constriction of the intestine. In all of these experiments small doses caused only constriction (figs. 2 and 6); as the quantity of adrenalin was increased, however, a prolonged and marked dilatation supervened on the preliminary constriction (see figs. 3 and 7). There were two exceptions, in which the least effective dose caused dilatation. These occurred during the early experiments, before we had fully realized the importance of completely removing gas from the lumen, and we consider it probable that this increase in volume of the loop was caused by the relaxation of the muscles of its walls, under the influence of the adrenalin.

The threshold for the constrictor effect was shown, in the six experiments in which it was determined, to vary within fairly wide limits, from 0.014 to 0.07 cc. adrenalin 1 : 100,000 per kilogram body weight, that is, it was reached by doses such as also caused a slight fall in blood pressure. The general resemblance of these two curves, indeed, make it at first glance appear possible that the one effect may be dependent on the other, and that the constriction in the intestine may be nothing more than a decrease of blood supply to its vessels, caused by the lowering of the general blood pressure. Latent periods, duration, and degree of decrease of intestinal volume, also bear some relationship to the same changes in the general blood pressure. Closer inspection of the tables (1 and 2), however, shows clearly that this is not the case. Though the diminution in intestinal volume generally occurs several seconds after the beginning of the fall of blood pressure, this is not always the case; for instance in experiments 13, 14, and 20, the records show the intestinal decrease to precede that of the blood pressure by several seconds, and our notes, made during the course of the experiments, corroborate this as actually occurring, and not being due to a possible faulty alignment. The time of the least intestinal volume does not correspond to that of the lowest blood pressure, nor is the duration of the constriction the same as that of blood pressure fall. (See experiments 7 and 13, where it is greater, and experiments 3, 18 and 20, where it is materially less.) Above all, the constriction does not take place only when the dose is such as to cause a fall of blood pressure; constriction of the intestine occurs time and time again when the blood pressure is above and not below its normal level (see figs. 3 and 7).

The dose of adrenalin necessary to cause a dilatation of the intestine to follow on this constriction is as variable as is the threshold dose for the constriction itself. It varies from 0.04 to 0.31 cc. of a solution 1 : 100,000 per kilogram in dogs, and in cats it is about 0.4 cc. The latent period of the dilatation is longer than that of the constriction.

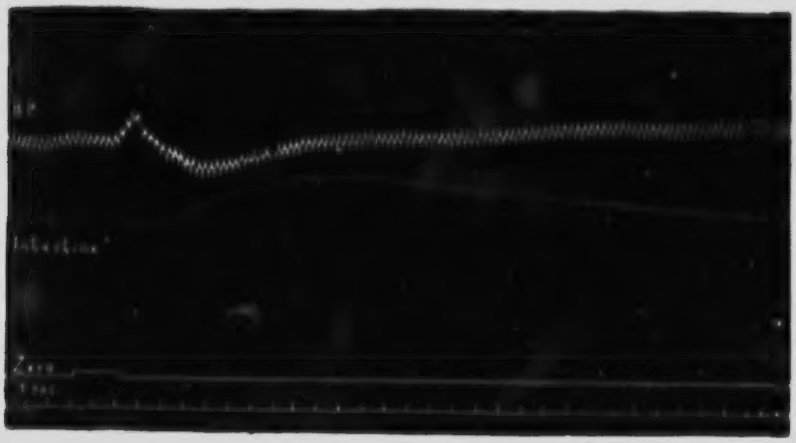

Fig. 3. Preliminary constriction followed by prolonged dilatation of the intestine, caused in the same animal as that of figure 2, by a larger dose (0.2 cc., 1 : 10,000) (Reduced ½)

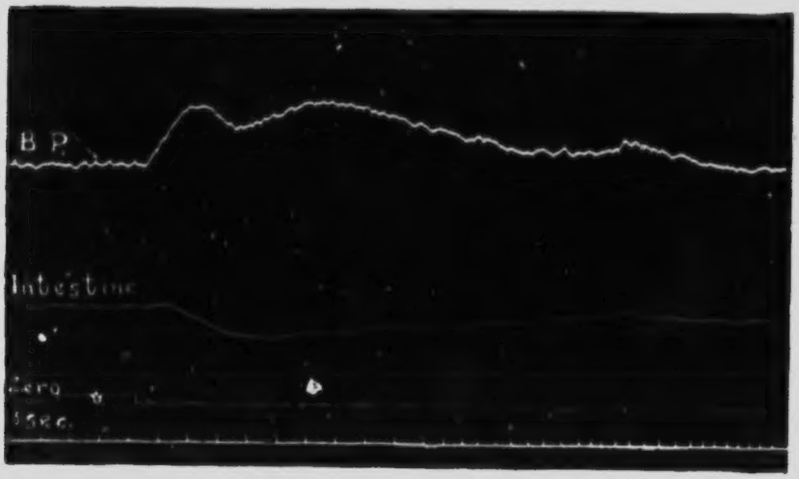

Fig. 4. Reaction of same loop of intestine as that of figures 2 and 3, to a dose of adrenalin of much the same magnitude (0.3 cc., 1 : 10,000) as that of figure 3, after the coeliac and superior mesenteric ganglia had been removed. (Reduced ½)

and the effect is as if the one were superimposed upon the other. As the doses are increased from the threshold dose on, the resulting constriction becomes more and more marked and its duration longer. Once the dose is great enough, however, to cause dilatation, this cuts short the first effect, with the result that the latter is reduced by from one-fourth to two-thirds of its former length. The volume change brought about by dilatation is much larger than that caused by constriction. For instance, in a dog of 25 kilograms the constriction reduced the volume of the system of the intestinal oncometer by 1 cc., while the dilatation increased it by more than 5 cc.

The observations on the resemblance of the curve of constriction to that of the general blood pressure may be applied in much the same way to this case also, for in increasing the doses of adrenalin sufficiently to cause a dilator effect in the intestine, in a few cases we crossed the threshold for pressor effect on the blood pressure. The same arguments, however, which prevented our accepting the explanation of a passive effect in construction, are also valid in this case. The latent periods of intestinal effect are longer than those of blood pressure fall, the time of maximum dilatation never coincides with that of maximum rise of pressure, and its duration is far greater, in many instances two to three times as long (experiments 21, 22, 23, table 2). As before, too, the occurrence of the intestinal effect does not depend on the nature of the blood pressure change; we have several records which, like experiments 3 and 7, show a marked increase in intestinal volume during a fall in general blood pressure.

As a possible explanation for the occurrence of increase in the intestinal volume, after injections of doses of adrenalin above a certain size, it might be suggested that such doses are just sufficient to affect the intrinsic nervous system of the intestine and to bring about relaxation of its walls, thus permitting expansion of the blood vessels within them. To investigate this, we inserted a rubber balloon into a part of the intestine immediately adjacent to that which furnished the loop in the oncometer, injected a small quantity of air, and connected it to a small bellows recorder, which made a tracing below the oncometer record. By this it was found that injections so small as to cause only a slight fall in blood pressure were sufficient to bring about a relaxation of the intestinal wall, and that as the dose was increased no well-marked difference could be observed in the reaction of the intestinal wall to that dose which first gave dilatation in the oncometer, nor to any of the succeeding ones.

In an attempt to decide upon the origin of this dilator effect of adrenalin we severed connection between the loop of intestine involved and the central nervous system, by dissecting and removing the two coeliac ganglia and the superior mesenteric ganglion, or by cutting the splanchnic nerves. In all experiments, five in all, after this operation was performed, the dilatation by adrenalin was entirely done away with, and doses which previously had caused a preliminary constriction followed by a dilatation now gave nothing but a simple constriction of the loop (see fig. 4).

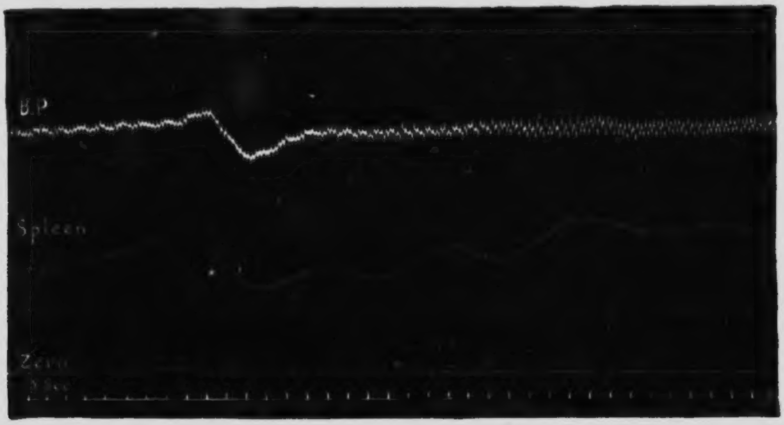

Fig. 5. Constriction in spleen, followed by a series of waves, after injection of a small dose of adrenalin (0.1 cc., 1 : 10,000). Dog 19 (Reduced ½)

THE SPLEEN

In the dissection of the spleen the gastrosplenic ligament with its numerous fat vessels was ligatured off, bit by bit, and cleared away from the neighborhood of the splenic blood vessels. In the early experiments those of the latter which supply the upper half of the spleen were also tied off. After two or three of these dissections, however, we were so dissatisfied with the appearance of the spleen under these conditions that we adopted a splenic oncometer with two lips. This enabled us to leave all vessels supplying the splenic substance intact, except sometimes that to the extreme tip of the upper end, which bound the organ too closely to allow of its being put into the oncometer. With the exception of this small piece, the spleen remained in excellent condition, even during the course of an experiment lasting over several hours. During dissection we protected it with saline pads, and we warmed the oncometer to receive it.

Of the dogs, ten in all, which we investigated, seven showed only constriction in the spleen in response to the whole range of doses of adrenalin employed. This constriction was more marked and more prolonged as the doses were increased in magnitude (see figs. 5 and 7). The three others each gave dilatation at some dose of adrenalin. Two of the three showed as a first effect dilatation with small doses; or, to speak more accurately, small doses of adrenalin set up in these

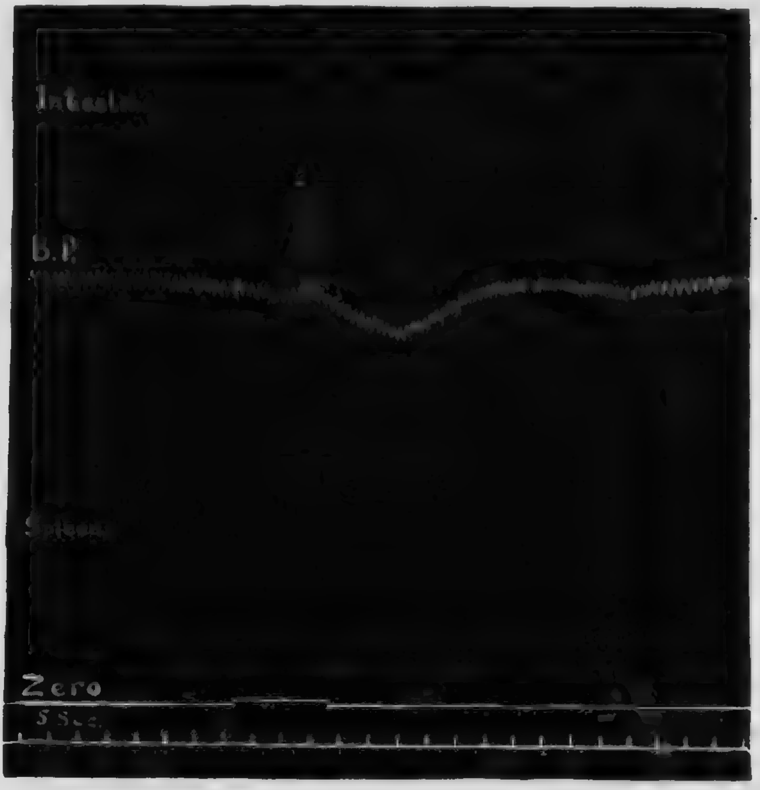

Fig. 6. Dilatation in spleen, and constriction in intestine, after small dose of adrenalin (0.3 cc., 1 : 10,000). Dog 21 (Reduced ½)

spleens (which had previously been relatively inactive) a series of waves, of which the first was in the direction of dilatation (see fig. 6). In both these organs the effect of increasing the dose was to increase the constriction in the waves at the expense of the dilatation, until large doses caused only decrease in volume. In the third of these spleens doses of adrenalin also set up series of waves, but its reaction differed

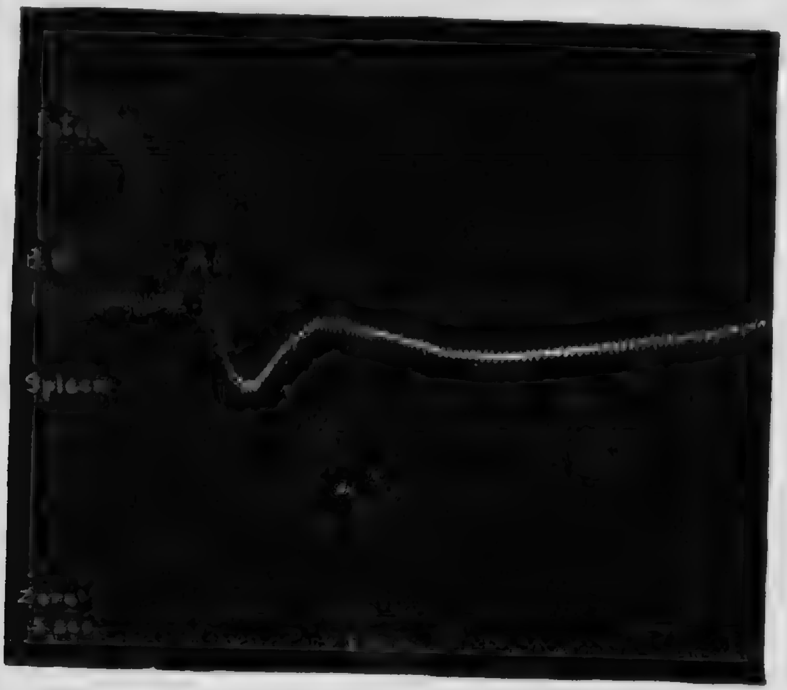

Fig. 7. Effect on same animal as that of figure 6, of a larger dose (1 cc., 1:10,000); slight dilatation followed by marked constriction in spleen, preliminary constriction and marked dilatation in intestine (Reduced ½)

rom that of the other two in that, on administration of relatively arge doses (0.2 cc., 1 : 100,000 per kilogram) the constriction was ollowed by dilatation.

KIDNEY

The upper part of the ureter and the kidney vessels of one side hroughout their entire length were dissected out to form a stalk. The esentery was removed as gently as possible from the surface of the kidney. A few of the larger veins running from it into the capsule were ligatured. During the dissection the kidney was protected as completely as possible with warm pads.

Four experiments in all were performed, two on cats and two on dogs. In every case injections of adrenalin caused constriction in the kidney (see figs. 8 and 9); with small doses of low concentration this was the only effect (see fig. 8); in two cases the preliminary constriction caused by large doses (e.g., 0.32 cc. 1 : 100,000 per kilogram), such as occasioned a preliminary rise followed by a fall of blood pressure, was followed by a dilatation of the organ. The curve of this dilatation was similar in form to that familiar to us in the reaction of the intestine to large doses of adrenalin. It showed a rise of

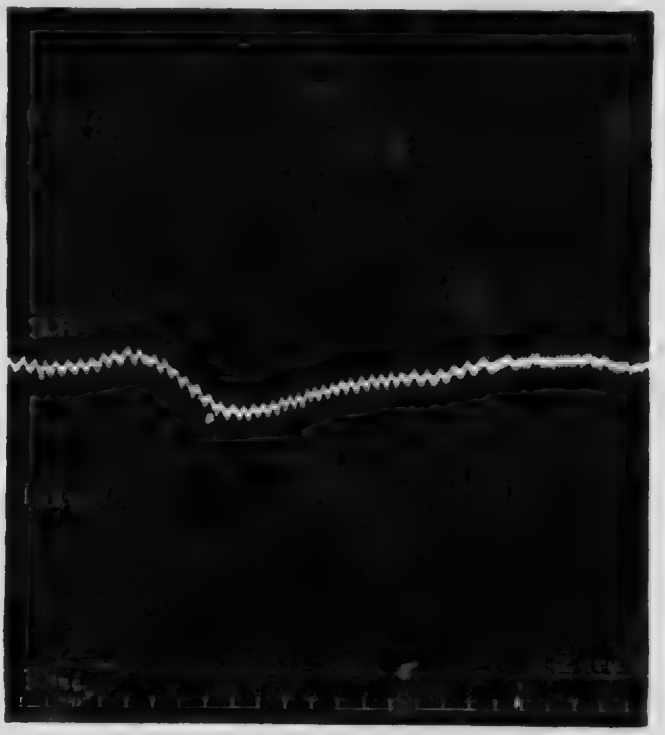

Fig. 8. Constriction of kidney after a dose of adrenalin 0.2 cc., 1 : 100,000 (Reduced ½)

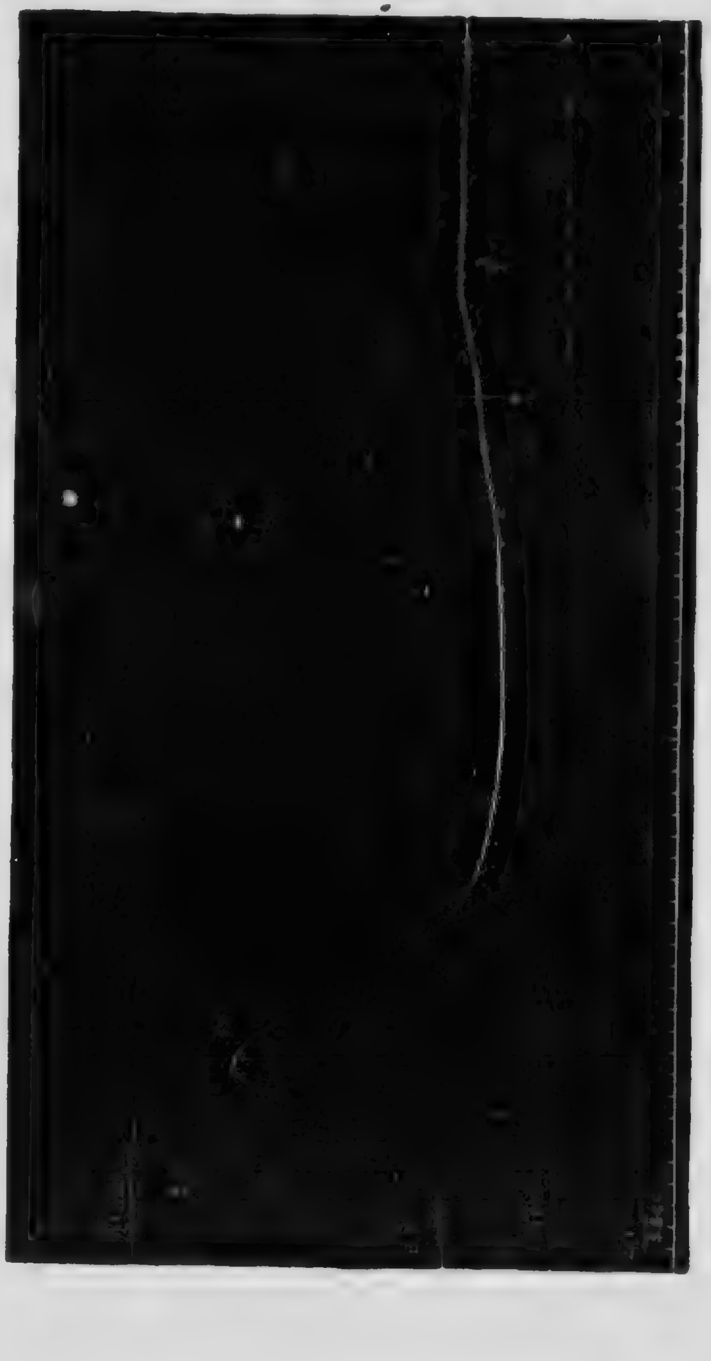

Fig. 9. Reaction of same kidney as in fig. 8, prelimininary dilatation and prolonged constriction, after larger dose (0.5 cc., 1 : 10,000) (Reduced ½).

the lever, which only gradually returned to the base line, not before 170 to 180 seconds had elapsed, and thus continued long after the blood pressure had regained its normal level. The cuase of the occurrence of this dilatation we were not able to determine.

In conclusion we wish to point out that the reactions of the various organs, though they may be of a similar nature, do not necessarily take place at the same time, nor for the same dose. Thus, for instance, in dog 23, table 2, though both kidney and intestine give constriction in response to small doses and dilatation in response to large ones, nevertheless that dose of adrenalin (0.4 cc., 1:100,000 per kilogram) which is enough to cause transition from a dilatation to a constriction in the intestine, still gives rise to nothing but a constriction in the kidney. Numerous other examples may be found by reference to that table.

That the output of adrenalin, which has been shown by the work of the last few years (3), (4), (5), to be so small during normal quiet life as to have no appreciable effect on blood pressure, is augmented during conditions of mental excitement, as well as by the asphyxia attendant on violent exercise, and by sensory stimulation, has been shown in a series of experiments by Cannon and the workers in his laboratory (6). The exact extent of this increase in secretion has not been determined, nor is it known whether it is sufficient to effect a rise rather than a fall in blood pressure. Elliott (7), in working on the secretion from the adrenal glands which is brought about by stimulation of the splanchnic nerves supplying them, has shown that in this case the quantity secreted is within the range of doses which have a depressor effect on the general blood pressure; whether this is also the case during the reflex stimulation of normal life, we are still ignorant. In any case, as shown by our experiments, the first effect of the outpouring of adrenalin during excitement must be to cause a constriction of the intestine and kidney, and generally, though not always, a similar constriction in the spleen. By this means there is brought about a shifting of the blood from these organs to the muscles, which, as Hoskins, Gunning and Berry (2) have shown, are at the same time actively dilated. If, as may prove to be the case, the output of adrenalin increases till the concentration in the arterial blood is of the order of about one-half or more than necessary to bring about a rise in blood pressure, a dilatation of the intestine, and perhaps also of the kidney, must take place, through the agency of some central mechanism, the location of which, and the source of stimulation to which, are as yet unknown.

TABLE 1

Shortening of the duration of intestinal constriction by the occurrence of dilatation

ANIMAL	WEIGHT	AMOUNT OF ADRENALIN INJECTED, CUBIC CENTIMETERS OF 1:100,000 DILUTION PER KILOGRAM OF BODY WEIGHT	LATENT PERIOD	MAGNITUDE OF CONSTRICTION	DURATION OF CONSTRICTION WHEN DILATATION IS ABSENT	DURATION OF CONSTRICTION WHEN DILATATION IS PRESENT	LATENT PERIOD	BLOOD PRESSURE CHANGE IN MILLIMETERS OF MERCURY	DURATION OF BLOOD PRESSURE CHANGE
	kgms.		*seconds*		*seconds*	*seconds*	*seconds*		*seconds*
Cat. 4........	3.15	0.06		Marked	160			Fall 136 to 110	160
		0.16		Marked		110		Fall 138 to 110	215
Cat 7........				Small	97			175 to 181 to 142	97
				Small		13		164 to 218	63
			12	Marked		28		170 to 225 to 151	240+
Dog 14........	7	0.03	11	Marked	32			102 to 90	33
		0.14	10	Very marked		28		90 to 87	23
		1.26*		Marked		15		96 to 180	106
Dog 20........	9.5	0.05	12	Marked	33		11	160 to 130	60
		0.31	10	Marked		21	11	150 to 122	37
		2.08	9	Very marked		12	7	52 to 182	210
Dog 21........	15	0.02	32	Marked	41		14	102 to 146	31
		0.67	11	Marked		29	8	106 to 122 to 86	30
		2.00	9	Marked		17	7	101 to 151	101

* All doses greater than 2 cc. adrenalin 1 : 100,000 were actually injected into the animal in a 1 : 10,000 concentration, but to make the dose comparable in the tables they are given in terms of 1 : 100,000 dilution; 5 cc. adrenalin 1 : 100,000 in the table was really 0.5 cc. adrenalin 1 : 10,000 in the experiment. This applies to both tables.

TABLE 2

A comparison of the effects of adrenalin on different organs in the same individual

ANIMAL	WEIGHT	AMOUNT OF ADRENALIN INJECTED CUBIC CENTIMETERS OF 1:100,000 DILUTION PER KILOGRAM OF BODY WEIGHT	EFFECT ON INTESTINE				EFFECT OF SPLEEN		EFFECT ON KIDNEY		EFFECT ON BLOOD PRESSURE	
			Constriction		Dilatation							
			Magnitude of constriction	Duration of constriction	Magnitude of dilatation	Duration of dilatation	Magnitude of change	Duration of change	Magnitude of change	Duration of change	Change in millimeters of mercury	Duration of change
	kgms.			*seconds*		*seconds*		*seconds*		*seconds*		*seconds*
Dog 11	15	0.03	None		Small	80	Small constriction	Persistent			152 to 147	45
		0.27	None		Marked	105	Marked constriction	230			174 to 187 to 142	87
		0.67	Small	15	Very marked	120	Very marked constriction	525			161 to 175 to 150	112
Cat 13	2.9	0.07	Small	83					Marked constriction	80	132 to 140 to 100	67
		0.35	Small	172					Very marked striction	210	80 to 92 to 68	115
		1.72	Marked	Persistent					Very marked constriction	285	106 to 213	63
Dog 21	15	0.01	No effect				Marked dilatation	50			160 to 148	20
		0.07	None		Small	130	Small dilatation followed by marked constriction				154 to 128	85
		2.00	Marked	17	Marked	210	Marked dilatation	160			102 to 172	125

Dog 22	25	0.02	No effect									
		0.20	Small	28	None		Small dilatation	48			132 to 123	44
		0.60	None		Marked	285	Marked constriction	Persistent			127 to 90	131
							Marked constriction followed by small dilatation	28			122 to 134 to 110	160
		1.00	Small	18	Very marked	312	Small constriction followed by persistent dilatation					
Dog 23	21.5	0.02	Barely perceptible	13		115			Marked constriction	100	143 to 121	30
		0.47	Slight	12	Small				Marked constriction	102	148 to 131	128
		0.93	None		Marked	Persistent			Marked constriction followed by dilatation	42	144 to 125 to 224	97

In investigating the dilatation occurring in various organs in the body under the influence of different concentrations of adrenalin in the blood circulating through them, we hoped to gain some light on the vexed question of the existence of dilator fibres in the sympathetic nerves to the blood vessels. The existence of these has been denied by many authorities, notably by Brodie and Dixon (8), and by Cannon and Lyman (9). On the other hand, evidence deduced from experiments of widely differing character has been brought forward in support of the theory that dilator fibers are present in the blood vessels, and are sensitive to adrenalin in solutions too dilute to stimulate the endings of the constrictor fibres. Dale's experiments on the reversal of the effect of adrenalin by ergotoxine (10), are interpreted to this effect by him. The pioneer work of Brodie and Dixon (8) on the lung already cited, and the later results of Desbouis and Langlois (11) and especially those of Enid Tribe (12) seem to point in this direction, the dilatation observed by Park (13), Elliott (17), and Cow (15), in coronary vessels, and that in vessels of other organs by Pari (16) and by Ogawa (17), in response to adrenalin offer further proof of the possibility of the existence of vaso-dilator fibres in the sympathetic system. On this subject our experiments have the value only of a negative finding, but as far as they carry us we have found no evidence of a direct stimulation of vaso-dilator endings by adrenalin, in any concentration approaching that which occurs under physiological conditions.

SUMMARY

1. Small doses of adrenalin cause constriction of the vessels of intestine, of kidney, and generally also of spleen.

2. The minimal dose necessary to produce this constriction is in much the same order of magnitude as that required to cause a fall in blood pressure, but it is not necessarily identical with it, nor is it the same for every organ in the same animal.

3. Increase of the dose of adrenalin causes in all cases marked dilatation of the intestine. This dilatation is brought about by doses materially less than those which are necessary to cause a rise in general blood pressure.

4. This dilatation in the intestine is under control of the central nervous system, and is done away with by severing connection with the central nervous system.

5. Adrenalin in the majority of cases has in all doses a constrictor

effect on the spleen; in some, minute doses cause first dilatation, which is the initial change of a series of rhythmical splenic waves.

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THE MECHANISM FOR VASODILATATION FROM ADRENALIN

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Up to the present, no satisfactory explanation of the vasodilatation resulting from adrenalin has been offered. That it might be of central nervous origin was indicated by the experiments of S. J. and C. Meltzer (1) in the dilatation of the vessels of the rabbit's ear from subcutaneous injection of adrenalin. They obtained nothing but constriction if the vasomotor nerves were cut. However the explanation of dilatation from subcutaneous injection of adrenalin in the rabbit is not necessarily the same for the cat because no dose of adrenalin causes a fall of blood pressure in the rabbit as it does in the cat.

Dale's (2) theory that small amounts of adrenalin stimulate vasodilator endings while larger amounts bring vasoconstrictors into play, is not supported by the observation that small amounts of adrenalin cause constriction while larger amounts cause dilatation of the intestine of the dog and cat (3). Nor does the hypothesis of Cannon and Lyman (4) satisfy the facts observed in the differential action of adrenalin (5). They attributed the two effects, vasodilatation and vasoconstriction to opposite actions according to the state of the muscle—relaxation when tonically shortened, contraction when relaxed.

Finally the work of Gruber (6) suggests that the central nervous system is involved in the dilatation from adrenalin. He found that doses of adrenalin which caused dilatation in the normal limb of the cat produced constriction when the nerves were cut.

In attempting to explain the dilatation from adrenalin in the intestine of the cat and dog we (3) found that if the splanchnics were cut constriction replaced dilatation. This observation led us into a study of the part played by the central nervous system in adrenalin vasodilatation. The following investigation is the result.

Ether anaesthesia was used in all experiments, except a few in which anocain was injected. Blood pressure in all except the anocain experiments was taken from the right carotid artery while adrenalin was injected into the left external jugular vein. The limb volume was registered by means of Brodie's bellows connected to a glass cylinder enclosing the part. Intestinal volume change was also indicated by a bellows recorder connected to the oncometer. Adrenalin chloride (Parke, Davis and Company) was freshly prepared for each experiment by diluting with distilled water.

PROOF OF AN ADRENALIN VASODILATOR MECHANISM IN THE CENTRAL NERVOUS SYSTEM

1. *By severing central nervous connection*

a. In the intestine. Volume changes in the small intestine were studied by methods described in a former research (3). The amount of adrenalin necessary to cause dilatation of the intestine was first determined. Connection with the central nervous system was then severed by cutting the splanchnics or by removing the coeliac and superior mesenteric ganglia. This caused obliteration of the intestinal dilatation from adrenalin and in all except one case it was replaced by prolonged constriction. Three dogs and four cats were studied. Connection with the central nervous system seemed to be necessary for the production of the intestinal dilatation occurring with larger doses of adrenalin. We say larger doses because occasionally there is dilatation resulting from small doses, which may be accounted for by the relaxation of the intestinal walls ((3), p. 316).

b. In the limb. Although both dogs and cats were employed in the study of limb dilatation, because of the greater proportion of skin to muscle vessels in the limb of the dog, cats served our purpose best. Hoskins, Gunning and Berry (7) have shown that the skin acts by constriction to small doses of adrenalin.

Simultaneous records were made of the volume changes of the two hind limbs after one limb had been denervated. In denervation the femoral and sciatic nerves were cut as high up as possible through slits in the skin, which were sewn up immediately after. In this way the part played by the central nervous system in the dilatation from adrenalin could easily be shown. The two cylinders were of the same size and enclosed approximately an equal volume of limb. Moreover the cuffs of the plethysmograph were placed high up on the limb so that muscle predominated over skin.

Small doses of adrenalin usually gave dilatation in the normal limb and constriction in the denervated limb. Large doses, such as those which usually produce a rise in blood pressure, caused constriction in both limbs. Ten cats out of fifteen gave this result. Four showed little or no change in the normal limb in response to small doses of adrenalin. That this failure of the normal limb to dilate might be due to a predominance of skin effects is not probable, for one of these limbs was skinned without modifying the reaction.[1]

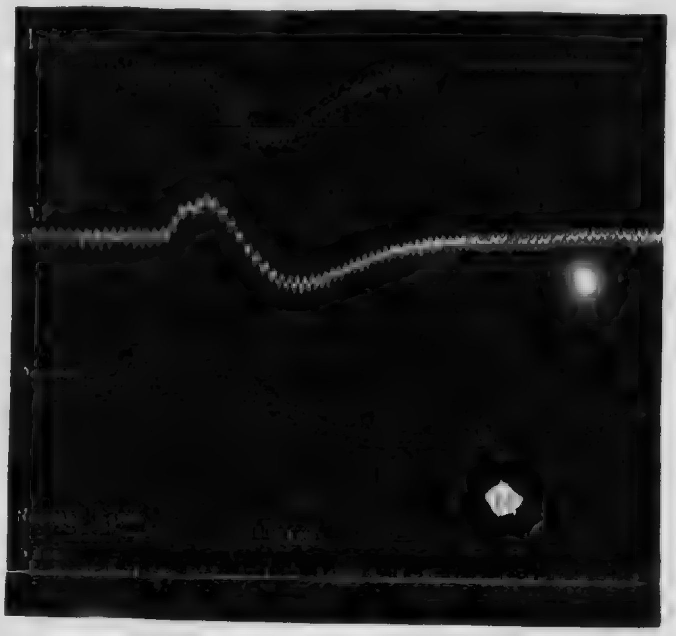

Fig. 1. Volume changes of normal limb, denervated limb and intestine in response to 0.6 cc. adrenalin, 1:100,000. Cat weighing 3.3 kgms. (Reduced ½.)

The fifth cat (weight 4 kgm.) which was an exception as far as the response in the normal limb was concerned, was the most sensitive to adrenalin of any cat which has come under our observation. Even

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[1] In order to determine the importance of the skin in volume changes in the cat's hind limb, we placed the two limbs of an animal which gave the typical limb dilatation in plethysmographs after one limb had been skinned excepting the sole of the foot. Dilatations from adrenalin were the same in both limbs. We concluded that if most of the hind limb was included in the plethysmograph, the skin reactions were negligible.

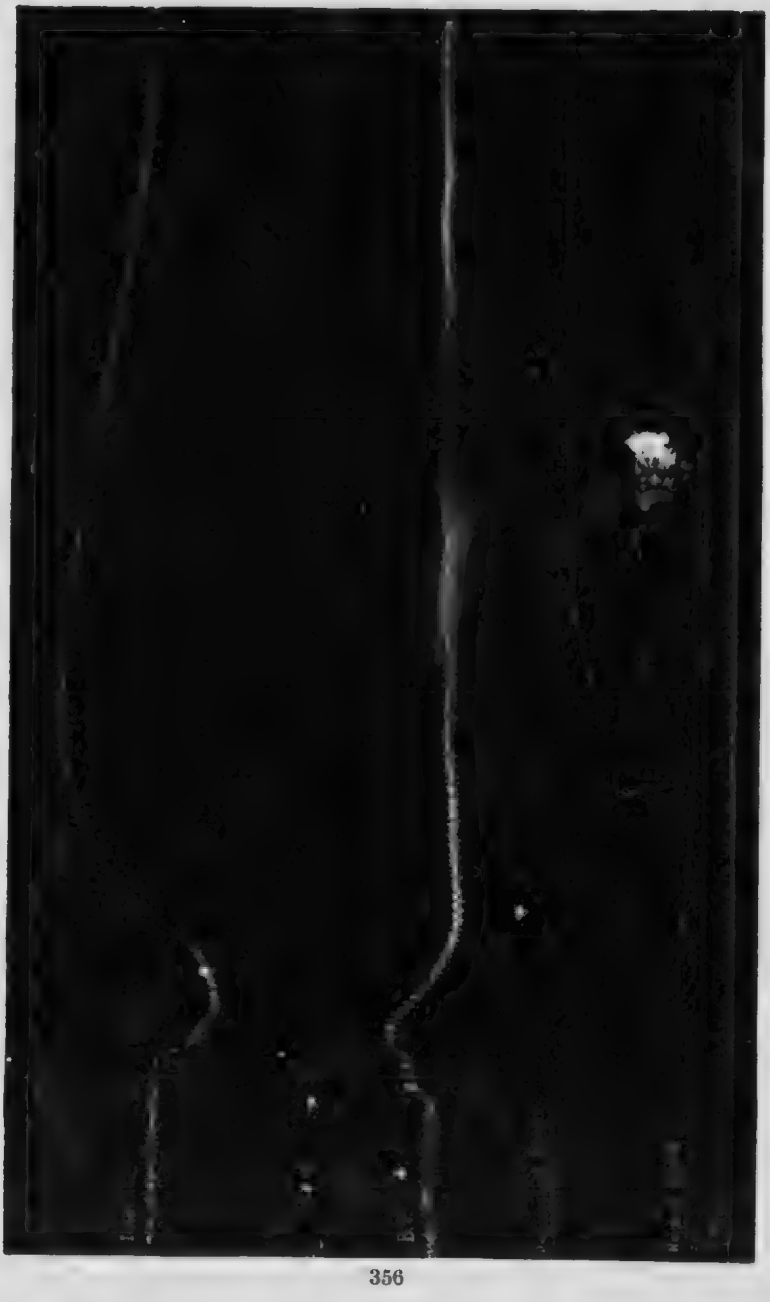

Fig. 2. Same as figure 1 in response to 2.0 cc. adrenalin, 1:100,000. (Reduced ½.)

0.025 cc. of adrenalin 1 : 1,000,000 caused a fall of blood pressure from 125 mm. to 120 mm., while 0.2 cc., 1 : 1,000,000 not only produced a fall of blood pressure from 127 mm. to 93 mm., but brought about constriction in both normal and denervated limbs. However, there is this to be said about these exceptional cases: the normal limb usually either gives no constriction or else much less constriction as compared to the denervated limb. So although there may be no positive dilatation there must be enough in the normal limb to lesson or else obliterate the local constrictor effect of adrenalin.

The following is a typical experiment of the ten which gave positive dilatation:

Cat, weight 3.3 kgms. (See figs. 1 and 2)

DOSE OF ADRENALIN cc. 1:100,000	BLOOD PRESSURE CHANGE IN MILLIMETERS OF MERCURY	NORMAL LIMB				DENERVATED LIMB			
		Dilatation		Constriction		Dilatation		Constriction	
		Amount	Duration	Amount	Duration	Amount	Duration	Amount	Duration
		cc.	*seconds*	*cc.*	*seconds*	*cc.*	*seconds*	*cc.*	*seconds*
0.2	118–127– 96	0.13	95	None		0.18	35	None	
0.4	118–131–100	0.33	178	None		0.16	31	None	
0.6	122–138–100	0.5	325	None		0.23	28	0.1	47
1.0	124–141–110	0.5		None		0.25	13	0.67	
1.5	127–153–117	0.34		None		0.15	11	0.9	275
2.0	127–157–113	0.13		None		0.10	9	1.4	
0.5 (1 : 10,000)	127–196– 89	0.13	18	0.63	74	0.12	5	1.45	265

The dilatation in the denervated limb was passive because it occurred at the same time that the blood pressure began to rise and lasted no longer than the rise. This dilatation was cut short or obliterated with larger doses of adrenalin. Dilatation in the normal limb came later than in the denervated limb and lasted as long as the blood pressure was below normal.

This difference in reaction between the denervated and normal limbs is not due, as Gunning (8) suggests, to extreme dilatation of the denervated limb resulting from the absence of vasoconstrictor impulses. A depressor substance obtained from ox pituitaries was injected into the animal that produced figures 1 and 2. The dilatation of the denervated limb was as great as that in the normal limb, showing that the limit had not been reached.

In one dog (17 kgm.) a plethysmograph was placed so as to include a hind limb just above the ankle. Adrenalin was injected into the circulation. As a result the limb was constricted as much as 0.66 cc. in one instance and as little as 0.3 cc. in another. Without disturbing the plethysmograph both femoral and sciatic nerves to the enclosed limb were then severed. The same amount of adrenalin (0.2 cc., 1 : 10,000) was injected as before with a resulting constriction of 1 cc. or more in every instance. Moreover the duration of constriction in the denervated limb was almost twice as long as that before cutting central nervous connection (fig. 4). The greater and more prolonged constriction, after the nerves were cut, was no doubt due to absence of dilatation from central nervous influence. This explanation also probably applies to one of the cats which failed to give dilatation in the normal limb, for the constriction in the normal limb was always decidedly less than in the denervated limb.

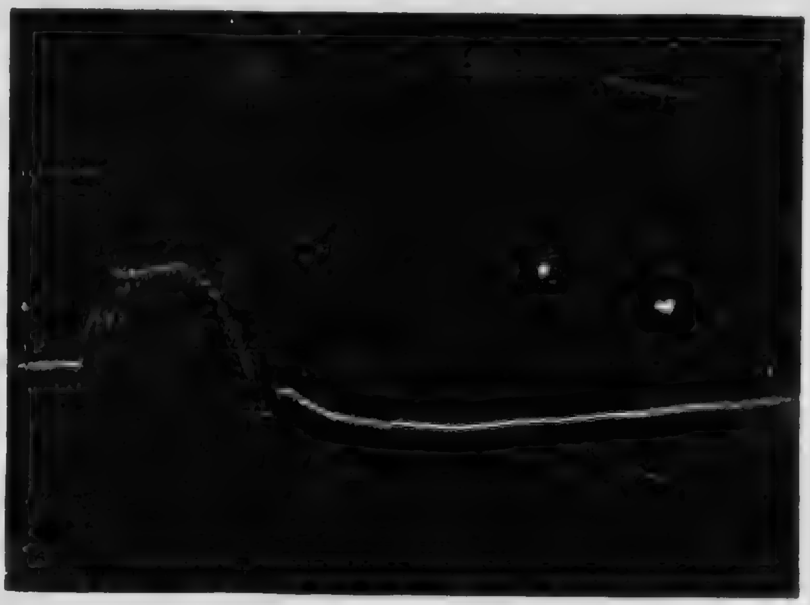

Fig. 3. Same as figure 1 in response to 0.5 cc. adrenalin, 1:10,000. (Reduced ½.)

We attempted to demonstrate the necessity of central nervous connection for dilatation from adrenalin in another way. The dose which gave the maximum fall in blood pressure was determined. A number of injections were made so that the average might be found. After cutting the nerves to the limbs the percentage fall in blood pressure from the same dose was ascertained. According to the evidence just submitted the percentage fall should decrease with every limb denervated.

Fig. 4. Increase of constriction in a dog's foot by destroying central nervous connection. *a*, Before cutting nerves; *b*, after cutting nerves (0.2 cc. adrenalin, 1:10,000; weight 17 kgms.). (Reduced ⅓.)

In the first animal, a cat weighing 1.3 kgm., 0.2 cc. adrenalin, 1:100,000 caused a fall in blood pressure of 18.7 per cent (from 123 mm.). After cutting the left brachial plexus the same dose produced a fall in blood pressure of 12.2 per cent, (from 114 mm.). Cutting the right brachial plexus reduced the fall to 9 per cent (from 100 mm.).

A cat weighing 2.3 kgms. responded to 0.1 cc. adrenalin, 1:100,000 by an 8 per cent fall in blood pressure (from 150 mm.), and to 0.3 cc. adrenalin, 1:100,000 by an average fall of 16.6 per cent (4 injections). When both brachial plexuses and both femoral and sciatic nerves had been cut the percentage fall from 0.1 cc. adrenalin, 1:100,000 was 2.7 while from 0.3 cc. adrenalin, 1:100,000 the average fall (4 injections) was 9.3 per cent (from 112 mm.), (see fig. 5).

Fig. 5. Blood pressure reactions to adrenalin (0.3 cc., 1:100,000) before and after cutting the nerves to the limbs. *a*, Before; *b*, after. Cat weighing 2.3 kgms. (Reduced ⅓.)

The above doses were so small that the intestine would scarcely contribute to the fall in blood pressure. After dilatation in the limbs had been prevented by destroying the central nervous connection there still remained the important back, chest, shoulder and hip muscles, which easily accounts for the large percentage fall still obtained. On the whole, this evidence tends to support our plethysmographic proof of a central nervous function in adrenalin blood pressure fall.

2. *By perfusion experiments*

A conclusive method of proving that the dilatation from adrenalin is due to a central nervous mechanism was devised. The part to be studied, limb or intestine, was cut off from the body circulation and perfused with warm oxygenated Ringer's solution. The nerves to this part were left intact. Dilatation of the part was ascertained by either the variation in outflow of the perfusing fluid or by means of a plethysmograph. Injections of adrenalin were then made into the body circulation and their effect upon the organ in question noted.

The prefusion fluid, oxygenated Ringer's solution or defibrinated blood mixed with Ringer's solution, was warmed by passing it through a tube enclosed in a cylinder through which warm water circulated. The apparatus was a modification of that described by Brodie and Cullis (9). A small thermometer inserted into the solution, by means of a T-tube, just before it entered the perfusion cannula enabled us to know the temperature as it started through the organ. Pressure was produced by compressed air led into the bottle containing the perfusion fluid. The pressure was controlled by means of a mercury valve.

The temperature of the liquid as it actually entered the organ was maintained in the neighborhood of 37°C. The pressure was usually somewhat below the general blood pressure.

To perfuse an intestinal loop without injuring its nerves large animals were almost necessary. A loop of intestine of a dog weighing 15 kgms. was perfused with a mixture of defibrinated blood and warm Ringer's solution after the circulation had been entirely cut off. The perfusion pressure was 120 mm. of mercury. The intestine was then enclosed in an oncometer. Injection of 0.5 cc. adrenalin, 1:10,000 into an external jugular vein caused a rise and fall in the blood pressure (136 mm. to 156 mm. to 93 mm.) and a dilatation in the intestinal loop which could in no possible way be reached by the adrenalin itself. A larger injection of adrenalin 2.0 cc., 1:10,000, caused a rise in blood pressure (97 mm. to 172 mm.) and a marked dilatation of the intestine. The dilatation of the intestine was accompanied by an increased outflow of the perfusion fluid.

We next prefused one hind limb of another dog (5.4 kgms.). The perfusion fluid was forced into the femoral artery and any change in the limb vessels was determined by measuring the outflow from the femoral vein. An injection of 0.2 cc. adrenalin, 1:10,000 caused an increase in the outflow from the femoral vein. In order to cut off the rest of the limb from the body circulation nearly all of the muscles were cut down to the bone, care being taken to leave the nerves intact. The same dose of adrenalin produced a decrease in the outflow. Apparently some adrenalin was still reaching the limb thus causing constriction and the vasodilator mechanism was perhaps inhibited by the vigorous operation of cutting the muscles.

The intestine and limb of a third dog (23.5 kgms. in weight) were perfused. The intestine employed was 20 cm. long. It could not be influenced directly by the adrenalin injected as it was entirely cut off from the body circulation; 0.7 cc. adrenalin, 1 : 10,000, injected into the jugular vein caused a dilatation of 0.28 cc. in the perfused intestinal loop; 3 cc. adrenalin, 1:10,000 into the general circulation produced a dilatation of 0.88 cc. in the loop. There was also a measurable increase in the venous outflow from the intestine.

One hind limb of this dog was included in a plethysmograph. The cylinder was large enough to include a major portion of the limb. Before its circulation was interfered with, 0.5 cc. adrenalin 1:10,000 injected into the general circulation caused a dilatation of 0.86 cc. (see fig. 6). Cannulae were inserted into the iliac artery and vein just below the bifurcation. The aorta was clamped considerably above the iliacs in order to prevent access of blood to the perfused limb by anastomoses. Ringer's solution at a temperature of 37°C. entered the limb by way of the iliac artery under pressure of 100 mm. of mercury. The same amount of adrenalin as before was injected into the general circulation. The first time the perfused limb dilated 0.68 cc. while at the second injection the expansion was 0.90 cc. In other words the amount of dilatation was about the same when circulatory connection was destroyed as when it was intact (see figs. 7 and 8).

The amount of dilatation varied with the dose; 0.25 cc., 1:10,000 gave 0.27 cc., while 1 cc., 1:10,000 gave 1.59 cc. After the limb had been perfused one and one-half hours, 1.0 cc. adrenalin, 1:10,000 into the jugular vein gave only 0.72 cc. dilatation. Another interesting

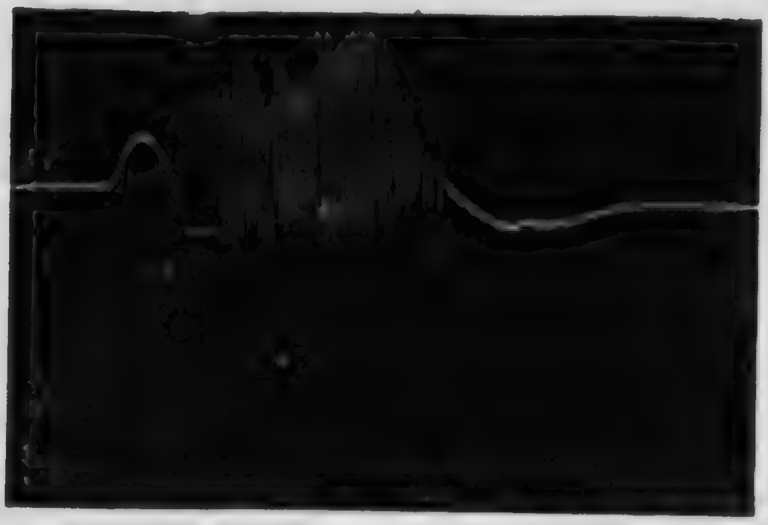

Fig. 6. Dilatation of a perfused loop of intestine, which has no connection with the body circulation, in response to adrenalin (3.0 cc., 1:10,000) injected into the jugular vein. Nerves to intestine undisturbed. Dog weighing 23.5 kgms. (Reduced ½).

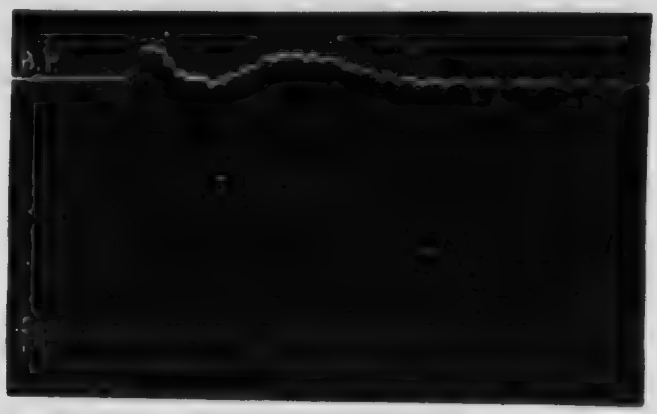

Fig. 7. Dilatation of a dog's hind limb in response to 0.5 cc. adrenalin, 1:10,000. Dog weighing 23.5 kgms. (Reduced ½.)

fact was the persistence of dilatation in the perfused limb. The intact limb returned to normal in sixty-five seconds when a dose of 0.5 cc. adrenalin, 1:10,000 was given, while the same limb perfused returned very slowly or not at all after a similar dilatation from adrenalin.

Thus we have proven both by cutting the nerves and by destroying the circulatory connection that the dilatation from adrenalin, in the intestine and in the limb, is due to some central nervous mechanism.

Fig. 8. Response of same limb as in figure 7, after connection with the body circulation has been destroyed. Perfused with oxygenated Ringer's solution. Nervous connection intact. Adrenalin (0.5 cc., 1:10,000) injected into jugular vein. (Reduced ½.)

INHIBITION OF THE ADRENALIN VASODILATOR MECHANISM

Although only about 5 per cent to 10 per cent of cats and dogs fail to give a fall in blood pressure with small doses of adrenalin, many of those animals are not normal in other ways. In a former study ((5) p. 443) three out of five such cases were diseased or emaciated while a fourth had been intoxicated with alcohol a few hours before. More recently we have investigated a case (cat weighing 2.4 kgms.), in which there was either only a slight fall or else no fall in blood pressure with doses of adrenalin as small as 0.1 cc. or 0.2 cc., 1:1,000,000. The intestine was placed in an oncometer and gave dilatation after the injection of 0.5 cc. adrenalin, 1:10,000 into the circulation. So in spite of the fact that there may be no definite fall in blood pressure, dilatation of the intestine may occur.

These observations kept us on the lookout for other conditions which might inhibit the adrenalin vasodilator mechanism. We found a cat weighing 4.3 kgms. which gave a fall in blood pressure of only 6 mm. (from 113 mm.) with 0.6 cc. adrenalin, 1:100,000. At the same time there was little or no effect on the volume of the normal limb. Associated with this poor response was a very dark venous-colored blood in the arteries. There had been no other signs of asphyxia. A plug of mucus in the trachea was found. Several minutes after the restoration of ventilation by removal of the mucus 0.5 cc. adrenalin, 1:100,000 produced a fall in blood pressure of 38 mm. from 140 mm. with dilatation of the normal limb. In this animal partial asphyxia seemed to produce incomplete inhibition of the adrenalin vasodilator mechanism.

Fig. 9. Reversal of blood pressure response to 0.5 cc. adrenalin 1 : 100,000, after injecting anocain. *a*, Before injecting anocain; *b*, after injection of anocain. Cat weighing 2.2 kgms. (Reduced ½.)

We had occasion to employ anocain (manufactured by Wingate Chemical Company, Ltd., Montreal) as a local anaesthetic in taking blood pressure from a dog's femoral artery. Injections of adrenalin in doses which in other animals gave a fall in blood pressure caused either no effect or only a rise in blood pressure. In order to determine whether the abnormal response was due to anocain a cat (weight 2.2 kgms.) was gently fastened to the board without its being alarmed. Then a solution of anocain (0.05 gram) was injected into the skin and later the muscles on either side of the femoral artery. Adrenalin, 1:100,000 was injected into the femoral vein. Blood pressure was registered from the femoral artery; 0.1 cc. caused a rise of 15 mm. from 180 mm.; 0.5 cc. increased the blood pressure 26 mm. from 192 mm., (see fig. 9). Following this the cat was placed under the influence of ether. Thirty minutes after the above reaction with anocain anaesthesia, 0.1 cc. adrenalin produced a fall of 10 mm. in blood pressure (from 175 mm.) while 0.5 cc. decreased the blood pressure 24 mm. (from 173 mm.).

One hour after anocain had been given, 0.5 cc. adrenalin produced a fall of 33 mm. (from 175 mm., see fig. 9). Anocain was again given intramuscularly after which adrenalin produced nothing but a rise in blood pressure.

After sufficient time had elapsed the fall in blood pressure again returned upon the injection of the usual dose of adrenalin.

This experiment was repeated in another cat with similar results. We would conclude that anocain inhibits the action of the adrenalin vasodilator mechanism.

There is some evidence that dilatation of a limb may be prevented by afferent impulses from that part. Many of the experiments which gave no dilatation from adrenalin in the normal limb were performed in a cold laboratory (15°C. or less). Although the operating table was warmed, the limbs were never as warm as the back of the animal. Because the temperature was much lower than in most of our successful experiments we thought that it might be the cause of a local inhibition of dilatation in the limb. Dilatation from adrenalin was occurring somewhere in the animal for there was a marked fall in blood pressure with the usual dose. The intestine was not dilating because the dose of adrenalin was below the intestinal dilatation threshold, moreover the loop of the intestine in the oncometer was constricting. We assumed that the dilatation must take place in the muscles which were kept warm, such as the back muscles. To investigate this assumption we warmed the normal limb with heat from an electric lamp. After the limb had ceased dilating from the artificial heat the usual dose of adrenalin injected into the general circulation caused an increase in volume of the limb. Previously the same doses of adrenalin produced either no effect or else constriction in the same limb.

It seems also that cutting the muscles in a limb may inhibit the dilatation from adrenalin. In one of the first perfusion experiments mentioned above, the response to the usual dilator-dose of adrenalin was changed to constriction by cutting part of the muscles of the thigh although the nerves were not injured.

BEHAVIOR OF THE ADRENALIN VASODILATOR MECHANISM

Simultaneous records of the volume changes of the intestine, normal hind limb and denervated hind limb together with the blood pressure in response to adrenalin, were obtained from thirteen cats. Whether the threshold dose for constriction in the normal limb was also the threshold dose for dilatation in the intestine could be answered in this manner.

Our apparatus showed that the threshold dose for dilatation in the limb was a little larger than the smallest dose causing a blood pressure fall, while the threshold dose for intestinal dilatation was usually four or five times as large as the threshold dose for the limb. Nor does the intestinal dilatation reciprocate the action of the normal limb for the latter usually continues to dilate some time after the threshold dose for dilatation of the former has been reached. Moreover there is an important distinction in the behavior of the limb and intestine. If we look at the effects on these respective parts with increasing doses we see that although the dilatation of the limb increases with increasing doses up to a certain point, beyond that the dilatation becomes less and less until constriction results. On the other hand constriction is the first adrenalin effect in the intestine, while with increasing doses dilatation appears and becomes larger and larger but is never replaced by constriction after the maximum is reached. Stated in another way, small doses of adrenalin act on the adrenalin vasodilator mechanism for the limb while large doses act on the adrenalin vasodilator mechanism for the intestine. Figures 1, 2 and 3 picture the results with increasing doses of adrenalin. The following experiment illustrates the foregoing statements:

Cat, weight 3.3 kgms.

DOSE OF ADRENALIN 1:100,000	BLOOD PRESSURE CHANGE IN MILLIMETERS OF MERCURY	NORMAL LIMB		DENERVATED LIMB		INTESTINE	
		Dilatation	Constriction	Dilatation	Constriction	Constriction	Dilatation
cc.		*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*
0.2	126–135–107	0.13			0.2	0.23	
0.6	124–140–106	0.26		0.15	0.6	0.5	
1.0	125–141–112	0.25		0.10	0.55	0.18	1.0
2.0	132–153–119	0.20		0.10	0.85	0.63	1.22
0.5 (1:10,000)	127–196– 89	0.13	0.63	0.12	1.45	1.22	2.34

AN INTERPRETATION OF THE ERGOTOXINE REVERSAL OF ADRENALIN ACTION

Dale (10) has shown that ergotoxine inhibits the action of the endings of constrictor fibers. Instead of assuming as Dale suggests that the fall in blood pressure from pressor doses of adrenalin after ergotoxine is due to stimulation of vasodilator endings, in the light of our present research we would interpret it in another way. We suggest that the fall is due to stimulation of the central vasodilator mechanism by adrenalin and failure to stimulate the constrictor endings because of their paralysis by ergotoxine. While constrictor endings function normally their total effect is greater than that of the vasodilator mechanism when pressor doses of adrenalin are injected. In a cat we were able to obtain evidence in support of this interpretation. We first determined the response of normal limb, denervated limb and intestine to adrenalin. Ergotoxine phosphate was given until the denervated limb which previoulsy had given constriction, gave no response to adrenalin. The normal limb still responded by dilatation. With larger doses of adrenalin the intestine dilated also.

There is additional evidence that our interpretation of ergotoxine reversal is correct, in the failure to obtain a reversal in the rabbit after ergotoxine (10). Unpublished work from this laboratory shows that the rabbit does not possess the adrenalin vasodilator mechanism; that is, adrenalin will not cause vasodilatation in the limb or in the intestine.

LOCATION OF THE ADRENALIN VASODILATOR MECHANISM

We have proven by experiment that destruction of the cerebrum does not prevent the vasodilatation from adrenalin.

A cat (2.8 kgms.) gave a fall in blood pressure of 29 mm. from 150 mm. with 0.2 cc. adrenalin, 1:100,000. After removal of the cerebrum the same dose produced a fall of 22 mm. from 114 mm. Further investigation is being carried on as to the location of the adrenalin vasodilator mechanism.

We have been able to show that the central nervous system is necessary for active dilatation resulting from adrenalin. Just how this mechanism is brought into action, it is impossible to say at the present time. The use of such a mechanism is obvious in case of muscle, but the object of vasodilatation in the intestine is not evident.

SUMMARY

1. Adrenalin vasodilatation in the intestine and limb is prevented by cutting the nerves to these organs.

2. A perfused limb or intestinal loop with nerves intact but without circulatory connection will dilate when the appropriate amount of adrenalin is injected into the general circulation.

3. Ill health, asphyxia, alcohol or anocain may inhibit the action of the adrenalin vasodilator mechanism.

4. Afferent impulses such as result from cooling or from cutting the muscles of a limb may impair or inhibit the adrenalin dilator reaction in that part.

5. The dilatation from adrenalin in a norma limb is produced by smaller amounts of adrenalin than those which cause intestinal dilatation.

6. Limb dilatation is replaced by constriction if the adrenalin is in sufficient quantity.

7. Intestinal dilatation is never replaced by constriction if the dose is above the dilatation threshold.

8. Ergotoxine reversal of adrenalin pressor effects is accounted for by paralysis of the vaso constrictors which mask the adrenalin vasodilator mechanism when large doses of adrenalin are used.

9. The adrenalin vasodilator mechanism is not located in the cerebrum.

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